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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/206,132	12/07/1998	GORDON J. FREEMAN	RPI-008CPDV	5096

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/206,132	FREEMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-63,71-74 and 76-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-63,71-74 and 76-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 01/02/02 in Paper No. 16 has been entered.

Amended and new claims 61-63, 71-74 and 76-94 are pending in the present application, and they are examined on the merits herein.

Following is a new ground of rejection.

Written Description

Claims 61 and 87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method for treating a subject with a tumor comprising modifying cells of the tumor *in vivo* to express a T cell costimulatory molecule, B7-2, to thereby treat the subject. The invention is also drawn to a method of

increasing the immunogenecity of a tumor cell comprising, modifying the tumor cell to express a B7-2 T cell costimulatory molecule such that the immunogenecity of the tumor cell is increased. The scope of the instant claims encompasses the utilization of any method step and any agent (e.g., any agent that induces or increases the expression of B7-2 on a tumor cell surface by increasing transcription, increasing translation, or increasing transport or stability of B7-2; any chemically coupled B7-2 agent; a nucleic acid molecule encoding B7-2) for modifying a tumor cell to express a B7-2 T cell costimulatory molecule. However, apart from the exemplification showing the transfection of tumor cells with a nucleic acid molecule encoding B7-2 molecule, the instant specification fails to teach a representative number of species for a broad genus of agents utilized to induce or increase the expression of B7-2 in a tumor cell in a method comprising any step for treating a subject with a tumor or for increasing the immunogenecity of a tumor cell *in vivo* as encompassed by the instant claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structures of a representative number of species for a broad genus of agents utilized to induce or increase the expression of B7-2 in a tumor

cell in a method comprising any step for treating a subject with a tumor or for increasing the immunogenecity of a tumor cell *in vivo*. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-62, 63, 71-74 and 76-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a mammalian subject having **a solid tumor**, comprising **direct injection** into cells of said tumor a nucleic acid encoding B7-2 molecule in a form suitable for expression of the B7.2 molecule in cells of said tumor and wherein **said B7.2 molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand** such that the

growth of said tumor is inhibited; the same method for modifying a tumor cell *in vivo* or for increasing the immunogenecity of a tumor cell *in vivo*, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 61-63, 71-72 and 88-94 are drawn to a method for treating a subject with a tumor comprising modifying cells of the tumor *in vivo* to express a T cell costimulatory molecule, B7-2, to thereby treat the subject; the same method wherein cells of the tumor are modified by delivering to the cells *in vivo* a nucleic acid molecule encoding for B7-2.

Claims 71-74 and 76-86 are drawn to a method of modifying a tumor cell to express a B7-2 molecule comprising transfecting a tumor cell with a nucleic acid molecule encoding a B7-2 molecule such that B7-2 is expressed by the tumor cell; the same method wherein the tumor cells are further transfected with at least one nucleic acid molecule encoding at least one MHC class II α chain protein and at least one MHC class II β chain protein, or wherein the tumor cells are further transfected with at least

one nucleic acid molecule encoding at least one MHC class I α chain protein, or wherein the tumor cells are further transfected with a nucleic acid encoding a β-2 microglobulin protein, or wherein the tumor cells are further transfected with a nucleic acid molecule which is anti-sense to a regulatory or a coding region of the invariant chain gene and thereby inhibiting the expression the MHC class II associated protein.

Claim 87 is directed to a method of increasing the immunogenecity of a tumor cell comprising modifying the tumor cell to express a B7-2 T cell costimulatory molecule such that the immunogenicity of the tumor cell is increased.

With regard to the elected invention, the instant specification discloses that tumor cells could be modified *in vivo* by introducing a nucleic acid molecule encoding B7-2 into the tumor cells for expression of the co-stimulatory molecule on the surface of tumor cells. Similarly, nucleic acid molecules encoding MHC class I or class II molecule or an antisense sequence of a MHC class II associated protein or the invariant chain gene (Ii gene) could also be introduced into tumor cells *in vivo* (See specification, pages 18-19). Example 5 shows that no tumor growth was observed upon intradermal or subdermal implantation of J558 plasmacytoma cells transfected *in vitro* with an expression vector containing cDNA encoding either mouse B7-2 or B7-1 molecule in syngeneic Balb/c mice. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons to be discussed below.

With respect to claims 61 and 87 encompassing modifying the level of B7-2 on a tumor cell by any method including: 1) transfection techniques; 2) treating the tumor cell

with any agent that induces or increases the expression of B7-2 on a tumor cell surface by increasing transcription, increasing translation, or increasing transport or stability of B7-2; 3) coupling B7-2 protein by any mechanism in any form to the tumor cell, the instant specification is not enabled for such a broadly claimed invention. While the specification is enabled for a method of direct injection into tumor cells a nucleic acid molecule encoding B7-2 (a transfection technique), the instant disclosure fails to enable for other methods of modifying the expression of B7-2 on a tumor cell surface for the reasons already set forth in the lack of Written Description section above. Additionally, the specification offers no guidance for a skilled artisan on how to identify which agents that will up-regulate the B7-2 expression on a tumor cell surface, the concentration of the agents utilized and their delivery mechanisms to ensure that an effective up-regulated expression level of B7-2 could be achieved to yield the desired therapeutic effects contemplated by Applicants. The specification fails to provide guidance on how to make and use any other agents apart from a nucleic acid molecule encoding B7-2 molecule to obtain the desired results. Nor does the present disclosure offer any guidance on any specific coupling agent that can be used to practice the presently claimed invention. Even if a skilled artisan could identify potential coupling agents known in the art, there is no support within the specification that coupling of B7-2 to the surface of a tumor cell provides a stable surface protein which functions as a co-stimulatory molecule for T-cells either *in vitro* or *in vivo*. The specification fails to identify which portions of a B7-2 protein should be used for any coupling method, nor does it provide any of the conditions under which coupling mechanisms should be

carried out. The specification also fails to provide any working examples (part of guidance) that coupling of the B7-2 protein by any method could function to produce the desired co-stimulatory signal to yield the therapeutic effects contemplated by Applicants. Therefore, it would have required undue experimentation for a skilled artisan to practice the instant broadly claimed invention in light of the unpredictability of expressing B7-2 on tumor cells by mechanisms other than transfection with a DNA encoding B7-2 such that a desired T cell co-stimulatory signal is generated, the absence of guidance provided by the specification for methods of expressing B7-2 on tumor cells other than transfection, the absence of working examples either *in vitro* or *in vivo*, and the absence of teachings in the prior art at the effective filing date of the present application with regard to B7-2 as a costimulatory signal.

With respect to claims encompassing the use of a nucleic acid molecule encoding B7-2 to modify a tumor cell, the nature of these claims falls within the realm of gene therapy, specifically *in vivo* gene therapy. At the effective filing date of the present application, the art of gene therapy was immature and highly unpredictable. In reviewing the state of the gene therapy art at about the time of the instant invention, Marshall (Science 269:1050-1055, 1995) stated that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1, lines 5-9 of the last paragraph) and that "with more than 100 clinical trials started and hundreds of millions of dollars at stake, the field is struggling to meet expectations" (page 1050, subtitle). In the same review article, NIH director Harold Varmus was quoted as saying "Despite the growing support for gene therapy, the field remains at a

very early stage of development. While there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patients – or even in animal models" (page 1050, column 2, first full paragraph). Even in a meeting review article on gene therapy and translational cancer research many years after the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) stated that "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement **to make gene therapy a reality**" (page 471, column 1, last sentence of first paragraph). Thus, it is clear that the art of gene therapy at the effective filing date of the instant invention was still immature, unpredictable and that the obstacles associated with gene therapy for achieving therapeutic effects could not have been overcome with routine experimentation. As the term "treating" encompasses various embodiments including the inhibition to eradication of a tumor growth, preventing or inhibiting a tumor metastasis or inhibiting the recurrence of a tumor, the instant specification is not enabled for such a broadly claimed invention. Apart from the exemplification showing that transfected J558 cells expressing B7-2 were unable to grow in naïve mice even after three weeks of intradermal or subdermal implantations, the specification does not provide sufficient guidance for a skilled artisan on how to achieve the full breadth of therapeutic effects contemplated by Applicants, particularly in light of the state of the gene therapy art discussed above. It is further noted that Colombo et al. (Cancer Immunol. Immunother 41:265-270, 1995) stated that "It is clear that tumor inhibition

and/or the induction of systemic immunity are not by themselves sufficient for evaluation of treatment efficacy and curative potential" (page 268, column 1, middle paragraph). This is because tumor inhibition has been studied by injecting tumor cell suspensions, and it is widely known in the art that tumor stroma plays an important role in tumor uptake, growth and progression; and therefore this situation differs from an established tumor nodules in a subject having a tumor. Colombo et al. further noted that the induction of systemic immunity with activation of cytotoxic T lymphocytes (CTL) might not be sufficient to destroy existing tumor cells growing in their own stroma for the various factors among which are the loss of MHC class I antigens by tumor cells and the impaired migration of CTL at the tumor site (page 268, column 1, second full paragraph). Furthermore, one of the Applicants (Dr. Lee Nadler) also raised a concern that T cells become tolerant of normally developing tumors, and as such costimulation could prove ineffective (Travis, Science 259:310-311, 1993; page 311, middle column). There is no evidence of record indicating or suggesting that the tolerance or anergy of T cells in a subject having a naturally occurring tumor has been overcome so that the breadth of therapeutic results contemplated by Applicants could be attained without undue experimentation. The physiological art is also recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Additionally, the Appeal courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*). It is noted that although claims 73-74 and 76-87 do not recite any therapeutic effects, when read in light of the specification the sole purpose for modifying a tumor cell *in vivo* (an embodiment of these claims) to express a B7-2 T cell costimulatory molecule is solely for treatment purpose.

The instant claims encompass any route of delivering a nucleic acid molecule encoding a B7-2 molecule alone or in combinations with a nucleic acid molecule encoding a B7 protein, a MHC class I or class II molecule, or an antisense sequence of the invariant chain gene into a subject having a tumor for treating or modifying or increasing the immunogenicity of tumor cells. Even for claim 88 specifically reciting local administration of a nucleic acid molecule encoding B7-2, the scope of the claim is not limited to the site of a tumor. Since the instant specification does not clearly define the metes and bounds of a local administration, the claim is reasonably interpreted as an administration of a nucleic acid molecule encoding B7-2 to any part of a body *in vivo* (local administration) as long as the nucleic acid molecule is delivered to cells of a tumor. At the effective filing date of the present application, *in vivo* vector targeting to desired cells, tissues or organs, for this instance tumor cells, continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art, including those published several years after the effective filing date of the present application. For examples, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types

of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) reviewed new techniques for gene delivery under experimentation in the art which show promise, but they are currently even less efficient than the viral gene delivery (see page 65, first paragraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that even several years after the effective filing date of the present application, resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia discussed the role of the immune system in inhibiting an efficient targeting of viral vectors such that an efficient transgene delivery and expression in target cells could not be achieved (see page 239, and second and third columns of page 242). The instant specification fails to teach a skilled artisan how to overcome the unpredictability for vector targeting *in vivo* known in the art such that an efficient gene transfer and expression of encoded molecules such as B7-2 protein, B7 protein, MHC class I or class II molecule, or an antisense sequence of the invariant chain gene could be achieved in tumor cells of a subject by any mode of delivery to attain the desired anti-tumor responses. In the absence of such guidance provided by the instant

specification, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

With regarding to claims 81 and 82, the specification offers no guidance for a skilled artisan on how to make and use any effective antisense nucleic acid molecule or any other effective agents to inhibit the expression of the invariant chain in tumor cells *in vivo* through the interference of its gene expression, mRNA translation, protein stability or intracellular transport to achieve any additional or synergistic therapeutic effects contemplated by Applicants. With respect to an embodiment comprising the use of an antisense molecule, it is well recognized in the art that many unwanted non-antisense effects are known to be associated with the antisense strategy (Branch A.D., TIBS 23:45-50, 1998). Although Branch noted that certain non-antisense effects can yield therapeutic effects, however, these non-antisense effects are not predictable even in 1998 and rules for rational design can not be applied to the production of non-antisense drugs and therefore they must be explored on a case-by-case basis (column 1, page 50). Furthermore, there are various obstacles known to the application of antisense molecules *in vivo* to achieve therapeutic effects as evidenced by the teachings of Stull et al. (Pharmaceutical research 12:465-483, 1995), Rojanasakul (Advanced Drug Delivery Reviews 18:115-131, 1996) and Plenat (Mol. Med. Today 3:250-257, 1996). Plenat stated that "the ability of oligonucleotides to inhibit genetic expression in a sequence-specific manner has been well documented", and "Extrapolation from *in vitro* studies to predict *in vivo* pharmacokinetics and effects in humans might be difficult and inappropriate. Animal models still remain an essential tool in the development of

oligonucleotides as efficient drugs in humans" (see abstract). Clearly, the attainment of therapeutic effects via any antisense molecule even several years after the effective filing date of the present application remains unpredictable and not routine. As such, given the complete lack of guidance provided by the instant specification for a skilled artisan on how to make and use any agent that inhibits effectively the expression of the invariant chain associated with an MHC class II molecule to yield the desired results contemplated by Applicants, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

With respect to claims encompassing modifying cells of non-solid tumors such as lymphoma and leukemia *in vivo*, the present specification offers no guidance for a skilled artisan on how to deliver an effective amount of a nucleic acid encoding B7-2 molecule into a sufficient amount of lymphoma or leukemia cells by any route such that a critical level of transfected cells could be attained to induce the desired anti-tumor effects. There are several obstacles to this application, some of which are already discussed briefly above. These include the adverse host immune reactions against the nucleic acid molecules encoding B7-2 to inhibit an effective level of said nucleic acid molecules to the desired cells, the dilution effect of the delivered nucleic acid molecules due to the circulation of lymphoma or leukemia cells in the blood system, and unlike localized solid tumors the T cell repertoire of the subject may already well be exposed to tumor antigens of lymphoma or leukemia and become anergized and as a result, costimulation with tumor cells expressing B7-2 could prove ineffective. It should be stressed that only tumor cells expressing an effective level of B7-2 could induce a T cell

anti-tumor response. This is supported by the teachings of Lenschow et al. (Proc. Natl. Acad. Sci. 90:11054-11058, 1993) showing that B7-2 is naturally present on antigen presenting cells such as dendritic cells and B cells, and therefore it is reasonable to assume that B lymphoma cells could naturally express some level of B7-2, but presumably at a level too low to induce any effective T cell anti-tumor response. With the lack of sufficient guidance provided by the instant disclosure, particularly the lack of any example showing that an effective expression level of B7-2 could be attained in transfected lymphoma or leukemia cells *in vivo* to induce an effective T cell anti-tumor response to yield the desired results contemplated by Applicants, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues raised above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 01/02/02 in Paper No. 16 (pages 6-12) have been fully considered.

With respect to the issue of any route of administration, Applicants basically argued that the instant invention does not require long-term transgene expression or widespread delivery to target tumor cells. The presently claimed invention only requires

a subset of tumor cells to transiently express B7-2 to yield a desired therapeutic effect, and that the anti-tumor immune response induced by the modified tumor cells is effective against both the modified tumor cells and unmodified tumor cells which do not express the costimulatory molecule. Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

Although examiner agrees with Applicants that long-term transgene expression and wide-spread transgene expression in target tumor cells may not be required for the presently claimed invention, a critical amount of target tumor cells expressing an effective level of B7-2 molecule is essential to generate an effective T cell anti-tumor response to yield the desired therapeutic effects. The instant specification offers no guidance or any working example showing that the critical amount of target tumor cells expressing an effective level of B7-2 could be achieved through *in vivo* gene therapy by any and all routes of delivery. Moreover, even several years after the effective filing date of the present application, *in vivo* vector targeting to desired cells remains unpredictable, and therefore therapeutic effects obtained through an effective transgene delivery and expression in target cells also remain unpredictable as evidenced by the teachings of Miller et al., Deonarain, Verma et al. Given the lack of guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the broadly claimed invention. Moreover, Applicants' arguments do not provide any factual evidence indicating or suggesting that obstacles associated with *in vivo* vector targeting have been overcome at the effective filing date of the present application such that induction of an effective T cell anti-tumor response

could be obtained *in vivo* by administering a nucleic acid molecule encoding B7-2 to a tumor cell by any and all routes of delivery. Lastly, Examiner would like to point out that the instant specification is enabled for a method of treating a mammalian subject having **a solid tumor**, comprising **direct injection** into cells of said tumor a nucleic acid encoding B7-2 molecule in a form suitable for expression of the B7.2 molecule in cells of said tumor and wherein **said B7.2 molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand** such that the growth of said tumor is inhibited; the same method for modifying a tumor cell *in vivo* or for increasing the immunogenecity of a tumor cell *in vivo*

With respect to the issue of utilizing an antisense molecule to inhibit the expression of the invariant chain in tumor cells in vivo to achieve the desired therapeutic effects, Applicants argued that a nucleic acid molecule which is antisense to the coding or regulatory region of the Ii gene has been previously described by Koch et al. Applicants' arguments are respectfully found to be unpersuasive because the mere disclosure of the primary structure of the murine Ii gene by Koch et al. does not indicate or teach which specific antisense sequence in the Ii gene would be or would not be effective for inhibiting the genetic expression of the invariant chain in tumor cells in a sequence-specific manner to yield the desired effects *in vivo*, particularly in light of the teachings of Branch, Stull et al., Rojansakul and Plenat discussed above. As such, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly, claims 61-62, 63, 71-74 and 76-94 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 61, 81 and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what is encompassed by the methods recited in claims 61, 81 and 87. There are no steps or agents recited for modifying cells of the tumor *in vivo* or a tumor cell to express B7-2 or to inhibit the expression of the invariant chain. The metes and bounds of the claims can not be clearly determined.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER